DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 18-422/S-040 and S-041

Pfizer Inc.
Attention: Rita Wittich
Vice President, Worldwide Regulatory Strategy
235 East 43nd Street
New York, NY 10017

Dear Ms. Wittich:

Please refer to your supplemental new drug applications, Supplement - 040 dated July 7, 2000, received July 10, 2000, and Supplement - 041 dated May 18, 2001, received May 25, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lopid (gemfibrozil) Tablets.

We acknowledge receipt of your submissions dated July 27 and August 3, 2001, to Supplement - 041.

Supplement - 040 provides for changes to the **Carcinogenesis, Mutagenesis, Impairment of Fertility,** and the **Pregnancy** subsections of the package insert to correct a typographical error found in a toxicology research report; i.e., delete references to an 0.6 times human dose in two paragraphs.

Supplement - 041 provides for changes to the **CONTRAINDICATIONS, WARNINGS,** and **PRECAUTIONS** sections of the package insert to strengthen the language regarding the concomitant use of gemfibrozil and HMG-CoA reductase inhibitors. In addition, specific symptoms reported with overdosage are added to the **OVERDOSAGE** section of the package insert.

1. In the **CONTRAINDICATIONS** section the following was added in bolded type:

   Combination therapy of LOPID with cerivastatin due to the increased risk of myopathy and rhabdomyolysis (see WARNINGS).

2. In the **WARNINGS** section the fifth warning was changed to the following:

   Concomitant therapy with LOPID and an HMG-CoA reductase inhibitor is associated with an increased risk of skeletal muscle toxicity manifested as rhabdomyolysis, markedly elevated creatine kinase (CPK) levels and myoglobinuria, leading in a high proportion of cases to acute renal failure and death. **Because of an observed marked increased risk of myopathy and rhabdomyolysis, the specific combination of LOPID and cerivastatin is absolutely contraindicated (see CONTRAINDICATIONS)**. IN PATIENTS WHO HAVE HAD AN UNSATISFACTORY LIPID RESPONSE TO

EITHER DRUG ALONE, THE BENEFIT OF COMBINED THERAPY WITH LOPID AND HMG-CoA REDUCTASE INHIBITORS OTHER THAN CERIVASTATIN DOES NOT OUTWEIGH THE RISKS OF SEVERE MYOPATHY, RHABDOMYOLYSIS, AND ACUTE RENAL FAILURE (refs. 7, 8, 9, 10) (see Drug Interactions). The use of fibrates alone, including LOPID may occasionally be associated with myositis. Patients receiving LOPID and complaining of muscle pain, tenderness, or weakness should have prompt medical evaluation for myositis, including serum creatine-kinease level determination. If myositis is suspected or diagnosed, LOPID therapy should be withdrawn.

3. In the **PRECAUTIONS: Drug Interactions** subsection, the paragraph concerning HMG -CoA reductase inhibitors was changed to the following:

   The risk of myopathy and rhabdomyolysis is increased with combined gemfibrozil and HMG-CoA reductase inhibitor therapy (see CONTRAINDICATIONS). Myopathy or rhabdomyolysis with or without acute renal failure have been reported as early as three weeks after initiation of combined therapy or after several months (refs. 7, 8, 9, 10). (See WARNINGS.) There is no assurance that periodic monitoring of creatine kinase will prevent the occurrence of severe myopathy and kidney damage.

4. In the **OVERDOSAGE** section the following sentence was inserted:

   Symptoms reported with overdosage were abdominal cramps, abnormal liver function tests, diarrhea, increased CPK, joint and muscle pain, nausea and vomiting.

We have completed the review of these supplemental applications, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed draft labeling. The enclosed draft labeling text consists of the draft package insert submitted August 3, 2001, from which the deletions regarding an 0.6 dose (per Supplement - 040) have been made.

Please submit the copies of final printed labeling (FPL) electronically to Supplement - 041 according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, these submissions should be designated "FPL for approved supplement NDA 18-422/S-041." Approval of these submissions by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call William C. Koch, R.Ph., Regulatory Project Manager, at (301) 827-6412.

Sincerely,

David G. Orloff, M.D.
Director
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research